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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,036	12/10/2001	Michel Koehl	017753-150	8634

7590 09/14/2006

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,036	KOEHL ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-34 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-34 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed June 30, 2006 is acknowledged and entered. Claims 19-34 and 36-38 are pending and under examination.

Claim Rejections - 35 USC § 103

The rejection of claims 19-38 as rejected under 35 U.S.C. 103(a) as unpatentable over Shabram *et al.* (WO 96/27677 A2, "Shabram") in view of Berg (WO 98/33572 A1), Bondoc *et al.* (*J. Indust. Micro. & Biotech.*, 1998, "Bondoc") and Georgiou et al. (US 6,027,888, "Georgiou") is maintained for reasons of record.

The claims amended are drawn to a method for purifying infectious adenoviral particles from a crude viral preparation comprising fluidized bed chromatography and gel filtration chromatography. The term "infectious adenoviral particles" encompasses infectious adenoviral vector particles. Specifically, the method involves contacting the preparation with particles of adsorbent in a fluidized bed, eluting the adsorbed adenoviral particles from the adsorbent particles and collecting the eluted adenoviral particles. The particles of adsorbent are comprised of an agarose matrix and a central core comprising quartz (Streamline®XL type or Streamline®Q XL type). Dextran chains are covalently coupled to the matrix, and positively charged groups (Q groups) are attached to the matrix. The support for the gel filtration chromatography step comprises alkyl dextran and methylene bisacrylamide matrix, or ethylene glycol and methacrylate matrix. Further limitations of the claims have been addressed previously.

Shabram teaches a method of purifying infectious recombinant adenoviruses (viral vectors for use in gene therapy) from a cell lysate comprising two chromatography steps (fluidized-bed adsorption followed by immobilized metal affinity column (IMAC) or hydrophobic interaction chromatography (HIB)), see abstract, page 4, lines 5-10, page 8, lines 4-8, and page 9, lines 13-15). *Recombinant adenoviral vectors are infectious in order to suitable for gene therapy applications, see Example IV.* Shabram uses a cross-linked agarose column (page 11, lines 27-28). The salt concentration of the eluant is diluted to about 450 millimolar or less in order to prevent premature stripping of viral particles from the exchange resin (page 12). A buffer is used to maintain the pH of the cell lysate solution between about 5.0 and 9.0. During chromatography, the resins are treated by flushing with NaCl and water. Shabram also discloses the production of adenoviral vectors from cell lines (page 15), lysis (page 17) and nucleic acid degradation (page 18). Shabram fails to teach the step of gel filtration and the specific type of adsorbent particle as instantly claimed.

Bondoc teaches a method of purifying infectious recombinant adenovirus (rAd5) using size exclusion chromatography, also called gel filtration (page 318, first column, third full paragraph). Georgiou discloses that alkyl dextran can be cross-linked with methylene bisacrylamide for gel filtration chromatography (col. 38, lines 44-65). It would have been obvious to use the materials described in Georgiou for Bondoc's gel filtration. One would have been motivated to use the materials because Bondoc's disclosure does not detail the specific materials to be used, and Georgiou provides a general description of the materials to be used in gel filtration. One would have had a reasonable expectation of success that the materials

described by Georgiou would have worked in Bondoc's gel filtration because Georgiou also uses the materials for gel filtration chromatography, as in Bondoc.

Berg teaches a method for adsorption of a substance from a liquid sample on a fluidized bed, in which the total yields are improved. The beads used in the method comprise a structure/ligand linked to a base matrix (bead) via an extender. The base matrix is comprised of cross-linked agarose (page 8, lines 28-33) and a bead filler of quartz (page 9, lines 30-31). Dextran is covalently bound to the agarose matrix (page 5, lines 2-17).

It would have been obvious to modify Shabram's method by substituting Bondoc's step of gel filtration with Shabram's step of IMAC. One would have been motivated by Bondoc's teaching that gel filtration chromatography can be substituted for zinc metal-chelating chromatography, a form of IMAC (page 318, first column, third full paragraph). One would have had a reasonable expectation of success that the gel filtration step would have resulted in purified adenoviruses because Bondoc reports that the adenovirus particles obtained by gel filtration were comparable with those obtained with the standard cesium chloride (CsCl) gradient-method page 318, first column, third full paragraph). It would have been obvious to use the adsorbent particles taught by Berg in Shabram's method. One would have been motivated to use Berg's adsorbent particles because Berg's method is aimed at improving total yields and productivity in adsorption processes on fluidized beds, and providing filler matrices that have improved breakthrough capacity in fluidized beds (page 4, lines 15-21). One would have had a reasonable expectation of success that the adsorbent particles of Berg would have improved Shabram's method because Berg's adsorbent particles are intended for use in methods of adsorption using fluidized beds.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that Shabram's disclosure regarding the use of fluidized bed chromatography is limited to an all-inclusive list that fails to render the claims obvious. Applicant notes that the working examples of Shabram's methods are directed exclusively to conventional packed bed chromatography.
    - In response, the fact that Shabram suggests the use of fluidized bed chromatography in one sentence in the whole document is not evidence that one of ordinary skill in the art would not have considered fluidized bed chromatography to be an alternate method. The teachings of Shabram are not limited to the working examples.
- Applicant argues that mere knowledge of fluidized bed chromatography techniques does not translate into predictability of success. In particular, Applicant argues that Berg's teachings actually lead one of skill away from using fluidized bed chromatography. Berg teaches that fluidized bed chromatography is normally limited to compounds having a molecular weight below 1,000,000 daltons. Applicant points to Exhibit C (Lennart Philipson, Structure and assembly of Adenoviruses, in Current Topics in Microbiology and Immunology, Vol. 109, 10, 1984) as evidence that adenovirus particles are entirely distinct from the type of macromolecules described by Berg (*i.e.*, polysaccharides, proteins, polypeptides, nucleic acids and synthetic water-soluble polymers). One would not have had a reasonable expectation of success with purifying adenoviruses because the

size of the adenovirus is about 150 fold above Berg's teaching that the normal weight is below 1,000,000 daltons.

- Applicant argues that Berg explicitly describes an upper limit for fluidized bed chromatography. Applicant asserts that the 10^6 dalton limitation taught by Berg does not correspond to the "usual" molecular weight but to the "upper size limit" beyond which Berg teaches that the fluidized bed is not effective. (The terms in quotes, "usual" and "upper size limit" are terms used in the Office action of 3/30/06, page 7). Applicant submits a dictionary excerpt that includes a definition of the term "limited" (Exhibit A), which in its ordinary sense stresses the existence of limits which are not, cannot, or may not be passed over. Applicant argues that because of the over 2 orders of magnitude difference between the molecular weight of an adenovirus particle and the upper size limit given by Berg, that a person of ordinary skill in the art would not have expected the fluidized bed chromatography to be effective for adenovirus purification.
    - In response to Applicant's arguments, the teachings of Berg have been carefully considered. If one were to consider Berg alone, the teachings of Berg would not be sufficient to motivate one of ordinary skill in the art to use fluidized bed chromatography for purifying adenoviruses. However, the Office and Applicant cannot ignore the fact that Shabram teaches a method of purifying infectious recombinant adenoviruses (viral vectors for use in gene therapy) from a cell lysate comprising two chromatography steps, one of which is fluidized-bed adsorption. Thus, even though Berg's teachings alone are insufficient to suggest the use of

fluidized bed chromatography for adenovirus particle purification, Shabram provides the suggestion and Berg provides the materials.

- Applicant further argues that the technical considerations and difficulties pertaining to purification of adenovirus particles are so great as to provide no reasonable expectation of success to use fluidized bed chromatography for adenovirus purification. Applicant points to Huyghe's article (*Human Gene Therapy*, 6:1403, 1995) as evidence that recovery of virus off a gel filtration column was very low, and that any purification process must preserve the integrity of each of the capsid proteins in order to result in infectious adenovirus particles. Applicant also points to Exhibit B (Protein Purification, Janson and Ryden, eds. (Wiley 1998)) at pages 148-149, which is submitted as evidence that it is well known in the art that anion exchange separation is based on ionic interactions between the negatively charged regions of the molecule being purified and the positively charged ligands attached to the chromatographic material. Applicant asserts that one skilled in the art would have anticipated that such parameters are distinct between a macromolecule and an adenovirus particles which exhibits at its surface more than hundreds of proteins interacting with each other through ionic, electrostatic and other interactions in order to maintain the virus structure.

  - In response to Applicant's arguments, the Office recognizes that there would be technical challenges faced when using fluidized bed chromatography for adenovirus particle purification. The question is whether one would not have been able to overcome these challenges to arrive at Shabram's suggestion to use fluidized bed chromatography. The evidence provided by Applicant is

insufficient to demonstrate that one would have had no *reasonable* expectation of success to carry out Shabram's suggestion.

- Applicant argues that Bondoc's teachings relating to purification of adenovirus are merely incidental and bare at best. Applicant argues that Bondoc does not teach at all which chromatographic material will result in successful purification of infectious adenovirus particles. Applicant asserts that Georgiou's teachings provide a general description of the material to be used in gel filtration. The reference to alkyl dextran/methylene bisacrylamide matrix disclosed in Georgiou is taught for the purification by gel filtration chromatography of recombinant proteins produced in bacterial cells. Applicant notes that the presently claimed method is directed to the production of infectious viral particles in eukaryotic cells, another technical field. Applicant asserts that in view of the art-recognized differences between proteins and adenovirus particles, differences that influence the gel filtration separation, there is no reasonable expectation of success that the gel filtration material taught by Georgiou in connection with recombinant proteins would in fact work for purifying adenovirus particles. Applicant further asserts that the contaminants that one would seek to remove during purification are also different between bacterial and eukaryotic producer cells, and that one would expect differences in the level of purity of the purified product.
    - In response to Applicant's arguments, the Office has considered Georgiou's teachings pertaining to gel filtration of protein produced in prokaryotes versus the instant invention's gel filtration of virus particles produced in eukaryotes. Given Bondoc's suggestion to purify adenoviruses with gel filtration, one of ordinary

skill in the art would use appropriate materials to do so. Looking to Georgiou for teachings regarding gel filtration would lead one to use any number of materials, including a dextran/methylene bisacrylamide matrix (col. 38, lines 44-65). Although Georgiou's teachings are in the context of recombinant proteins produced in prokaryotes, one would have been motivated to use a dextran/methylene bisacrylamide matrix because of its known ability to separate different sized molecules by providing varying pore sizes. Georgiou also teaches that the size of the cross-linking molecule can be increased to obtain larger pore sizes. Given the ability of a dextran/methylene bisacrylamide matrix to separate different sized molecules, one would *reasonably* expect adenovirus particles to be capable of being separated by the matrix. Therefore, the rejection is maintained for reasons of record.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 9/11/06

STACY B. CHEN
PRIMARY EXAMINER